REMARKS

In response to the Office Action mailed October 3, 2006, Applicants have the following remarks:

Applicants have amended the specification, in particular paragraph [0050] to include the nucleic acid and amino acid sequences of human MIS which were incorporated in the present application by specific reference to U.S. Patent No. 5,047,336. Applicants have also included the amino acid and nucleic acid sequences of the C-terminal fragments of human MIS which were incorporated in the present application by specific reference to Fig 18 of U.S. Patent No. 5,661,126. Accordingly, no new matter has been added by virtue of the amendments to the specification and their entry is respectfully requested.

Applicants have amended the claims to expedite prosecution. Claims 1 and 18 have been amended to (i) define MIS having the amino acid sequence of SEQ ID NO:5 or 6, (ii) to make it clear that the decreased side-effects refer those associated with interferon γ administration, and (iii) to indicate the effective amount of interferon relates to the amount of interferon γ that results in its decreased side-effects. Claims 1 and 18 have also been amended to limit the administration of interferon to administration of interferon γ. Accordingly, Claims 12, 13, 29 and 30 have been cancelled. Claims 9 and 26 have been amended to define the C-terminal fragment as 108 amino acids or more C-terminal amino acids of MIS, or the amino acid sequence as SEQ ID NO:11; and Claims 8, 11, 25 and 28 have also been amended to define the term rhMIS. Accordingly, no new matter has been added by virtue of the amendments to the claims and their entry is respectfully requested.

Claim Rejection:

Claims 1-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards to the invention.

To support this rejection, the Examiner asserts that reciting the terms "MIS" and "rhMIS" are the sole means of identifying the polypeptides of the claimed methods and that this renders the claims indefinite because different laboratories used the same laboratory designations to define completely distinct molecules. Applicants respectfully disagree and submit the terms "MIS" and "rhMIS" are well known to the skilled artisan. However, to expedite prosecution the Applicants have amended the claims.

Applicants respectfully submit amendments to claims include MIS "having the amino acid sequence of SEQ ID NO:5 or 6 and a fragment thereof" obviates this rejection. The applicants disclose in the specification reference to the complete nucleotide sequence for MIS, citing U.S. Patent application

5,047,336 which is incorporated by reference in their entirety (see paragraph [0050] and [0217]). Applicants have amended paragraph [0050] of the specification to make it clear that the complete nucleotide sequence for human MIS corresponds SEQ ID NO:1 as disclosed in U.S. Patent No. 5,047,336 on column 4, line 14 to column 9, line 10. Applicants also submit amendments to paragraph [0050] the specification to incorporate the amino acid sequence of MIS which is incorporated by reference in U.S. Patent No. 5,047,336, making it clear that SEQ NO:5 is the complete amino acid sequence of human MIS protein, and SEQ ID NO:6 is the complete amino acid sequence of mature human MIS protein.

Applicants respectfully submit amended Claims 1 and 18 to define the MIS has the amino acid sequence of SEQ ID NO: 5 or 6. Applicants respectfully submit amendments to claims 8, 11, 25 and 28 to define the term rhMIS has obviated the rejection which therefore should be withdrawn.

Applicants showed that one can use MIS to increase anti-tumor effect of interferon. Namely, in Example 3 (see paragraph [0178]), a recombinant human MIS or "rhMIS" is used. Also taught in the specification in paragraph [0053], is the term "recombinant MIS" which refers to MIS polypeptide, or fragment thereof, including the C-fragment, that is prepared using recombinant means. Accordingly, the skilled artisan would know from the specification and from the exemplification that a wide range of MIS polypeptides and functional derivates of MIS could be used in the methods of the present invention.

The Examiner further assets the term "decreased side-effects" used in Claims 1 and 18 are indefinite as it is unclear to what side-effects are decreased. The Applicants respectfully submit, as amended, claims 1 and 18 make it clear to the skilled artisan that the decreased side-effects refer those associated with interferon γ administration. Interferon side-effects of are disclosed in paragraph [0076], and the effective amount of tumor inhibiting interferon is an amount that results in decreased side effects is disclosed in paragraphs [0012] and [0088]. Thus the amendments to the claims do not constitute new matter and obviate the rejection. Accordingly, Applicants respectfully submit that the amendment has obviated this rejection.

The Examiner further supports the rejection under 35 U.S.C., second paragraph citing the term "substantially free of N-terminal fragment" in Claims 9 and 26 is indefinite because the term "substantially" is not defined by the claims and that the specification does not provide a standard for ascertaining the degree to which substantially refers to. Applicants respectfully submit amendments to claims 9 and 26, which is supported by paragraph [0048] in the specification, where Applicants teach the C-terminal fragment of MIS refers to the C-terminal fragment as a result of proteolytic cleavage (e.g plasmin cleavage) of the full length MIS. C-terminal fragments are also disclosed in paragraph [0050] by reference to Figures 17 and 18 in U.S. Patent No. 5,661,126 which is incorporated by reference in the

patent application obviate the rejection. Applicants submit amendments to paragraph [0050] in the specification to make it clear the C-terminal amino acid sequence of human MIS is referred to as SEQ ID NO: 11 in the present application (which corresponds to SEQ ID NO:4 in the U.S. Patent No. 5,661,126) and the C-terminal nucleotide sequence of human MIS is referred to as SEQ ID NO:12 (which corresponds to SEQ ID NO:3 in the U.S. Patent No. 5,661,126).

Accordingly, the Applicant respectfully submits that the claims as amended obviate the rejection under 35 U.S.C., second paragraph and that the rejection of claims 1-34 should be withdrawn.

Claim Rejection:

Claims 1-16 and 18-33 are rejected under 35 U.S.C.102(b) as being anticipated by Donahoe at al (US Patent 5,661,126; 8/26/1997).

To support this rejection, the Examiner summised on page 7 of the office action that Donahoe at al teaches a method comprising administering MIS and interferon to a patient having a tumor selected from the group consisting of vulvar epidermal carcinoma, cervical carcinoma, endometrial adenocarcinoma, ovarian adenocarcinoma, ocular melanoma, prostate tumor, breast tumor, cutaneous tumor or germ cell tumor.

Applicants respectfully disagree and request that this rejection be withdrawn for the following reasons.

Applicants disagree with the statement made by the Examiner that "the method taught by Donahoe et al. would result in decreased side-effects, thereby increasing anti-tumor effect of interferon" (page 7, lines 10-11 of the Office Action). Applicants agree that Donahoe et al., teaches the administration of chemotherapeutic agents to increase the anti-tumor effect of MIS in the use of MIS for the treatment of tumors. Donahoe et al. states a "chemotherapeutic agent, which combined with MIS will have an additive effect on the treatment of the tumor" (line 66, col 20 to line 2, col 21). In other words, a chemotherapy agent used with MIS increases the total effect of MIS on the treatment of the tumor as compared to the use of MIS alone. In the extensive list of chemotherapeutic agents disclosed by Donahoe at al, the only interferon listed is interferon α (Col 21, line 34) not interferon γ as currently claimed. Furthermore, Donahoe et al., specifically disclose interferon (α, β or γ) as examples of agonists of MIS (Col 26, line 35), defining agonists as "an agent which enhances the physiological response of an organ or organism to the presence of a second agent. Thus an agonist of MIS increases the effectiveness of MIS by increasing an individuals response to the presence of MIS" (Col 26, lines 28-32). In other words, Donahoe et al. teach the use of interferon (α, β or γ) to increase effectiveness of MIS. This is the exact opposite of the

present invention; the use of MIS to increase the effectiveness of interferon γ. Donahoe et al. does not teach the use of MIS to increase effectiveness of interferon γ. In particular, Donahoe et al., does not teach the use of MIS to augment the anti-tumor effects of interferon γ, nor does Donahoe et al., teach the use of MIS to reduce the dose of interferon γ in the use for the treatment of cancers. Accordingly, there can be no anticipation.

Furthermore, Donahoe et al. does not teach any doses of administration of interferon γ and thus does not anticipate the present invention of an effective amount of interferon γ, where the effective amount is a lower dose than the amount given conventionally, e.g. less than $1x10^6$ International Units per administration, as disclosed in [0088] of the present application.

Applicants submit amendments to Claims 1 and 18 to limit the administration of interferon to effective amounts of interferon γ to expedite prosecution.

Claim Rejection:

Claims 1-34 are rejected under 35 U.S.C.103(a) as being unpatentable over Donahoe at al (US Patent 5,661,126;. 8/26/1997) in view of Cohen (Int. J. Radiation Oncology Biol. Phys., 2/87, 13(2):251-258).

The Examiner asserts the combined teachings of Donahoe "to administer MIS and interferon to a cancer patient" and Cohen to "optimize the amount to MIS and interferon in said administration" (Office Action, mailed October 3, 2006, page 10) would be obvious to one of ordinary skill in the art at the time of the invention. The Examiner also contends that "one would be motivated to administer interferon below $1x10^6$ International Units per administration since Donahoe et al., a lower dose of interferon, in combination with MIS administration would predictably treat tumors" and that one would have a reasonable expectation of success in performing the claimed methods since administration of MIS and interferon is well known and conventional in the art.

The Examiner asserts Donahoe et al., teaches a method comprising administering MIS and interferon to a patient having a tumor, as mentioned above, and also teaches that a chemotherapeutic agent is for example interferon α. The Examiner also states that such a chemotherapeutic agent administered with MIS will have an additive effect on the treatment of tumor, and that such chemotherapeutic agent can be reduced from the manufactures recommended dose, thereby reducing undesirable side-effects.

Applicants respectfully disagree and request that this rejection be withdrawn for the following reasons. As mentioned above, Donahoe et al., teaches only that chemotherapeutic agents have an additive

effect on the use of MIS for treatment of tumors, but does not teach the use of MIS for an effect on the use of chemotherapy, in particular the use of interferon γ to treat tumors.

Thus, Applicants respectfully submit that if one skilled in the art were to combine Donahoe et al., and Cohen et al., one would not arrive at the claimed invention, e.g. the use of MIS, or a C-terminal fragment of MIS, to augment the anti-tumor effects of interferon γ. The cited reference, alone or in combination, provides no teaching or suggestion that would direct the skilled artisan to use MIS to reduce the effective dose of interferon γ for the treatment of cancer and thus attenuate the interferon γ-associated side effects.

Applicants respectfully submit that, prior to the present invention, methods to reduce the side effects of interferon γ were not known. Without such knowledge, Applicants assert that combining and modifying Donahoe and Cohen in order to practice the claimed invention would not have been reasonably expected to succeed at the time of the present invention. In view of all the deficiencies in the prior art, Applicant respectfully submits that the Examiner has not established a prima facie case of obviousness.

Accordingly, Applicant respectfully requests that the renewed rejections of claims 1-34 under 35 U.S.C. 103(a) be withdrawn.

In view of the foregoing, Applicant respectfully request favorable reconsideration of the application.

The Commissioner is authorized to charge any fee deficiencies or credit any overpayments associated with this submission to the Nixon Peabody LLP Deposit Account No: 50-0850.

The Examiner is invited to contact the undersigned if further matters need to be discussed in order to expedite the prosecution of the present application.

Date: 3/26/07

Respectfully Submitted,

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